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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/661,398	09/12/2003	H. Robert Horvitz	01997/548003	7921

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EXAMINER	
HIBBERT, CATHERINE S	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/661,398	HORVITZ ET AL.	
	Examiner	Art Unit	
	Catherine S. Hibbert	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *5-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office action on the Merits of the application filed 12 September 2003, which claims benefit of the Provisional Application Nos. 60/437,821 filed 2 January 2003 and 60/410,160 filed 12 September 2002. Claims 1-21 are pending. Claims 1-4 are under examination. Claims 5-21 are drawn to non-elected inventions/species and are withdrawn.

Election/Restrictions

Applicant's election without traverse of the invention of Group I, claims 1-4 in the reply filed on 11 January 2007 is acknowledged. Claims 1-21 are pending.

Claims 5-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11 January 2007.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows: The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, Application Nos. 60/437,821 and 60/410,160 fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Claim 1, step (a) recites "contacting a cell comprising a mutation in a Class B synMuv gene selected from the group consisting of: *mep-1*, *lin(n3628)*, *lin(n4256)*, and *lin-65*...". While the disclosure of the instant application provides support for the genes *lin(n4256)* and *lin-65,* the Provisional Applications 60/437,821 and 60/410,160 do not provide any support for the *lin(n4256)* and *lin-65* genes as there is no mention of either of these genes in the Provisional Applications. Therefore, claim 1 and claims 2-4, which depend from claim 1, do not receive the Priority dates of the provisional applications.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are incomplete for omitting an essential step. While all of the technical details of a method need not be recited, the claims should include enough information to clearly and accurately describe the invention and how it is to be practiced. The minimum requirements for method steps minimally include a contacting step in which the reaction of the sample with the reagents necessary for the assay is recited, a detection step in which the reaction steps are quantified or visualized, and a correlation step describing how the results of the assay allow for the determination. In claim 1, the correlation step is missing. Claims 2-3 are incomplete insofar as they depend from claim 1.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification defines the genes for *lin(n3628)*, *lin(n4256)*, *lin-65* and *mep-1*, as nucleic acids "substantially identical" to SEQ ID No's: 24, 27, 28 and M04B2.1, respectively (specification p.16, lines 9-10, 14-15, 19-20 and p.17, lines 24-26). A skilled artisan would not be able to ascertain the meaning of the term "substantially identical" in the context of the genes named in claim 1. It is not clear what nucleic acid sequence homology with the sequences having SEQ ID No's: 24, 27, 28 and M04B2.1 would be required to meet the limitation "substantially identical". Claims 2-4 are indefinite insofar as they depend from claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.
>
> Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:
>
> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for

written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to "a synthetic multivulval gene, or an ortholog thereof". The specification (p.47) describes an ortholog as any gene that encodes a molecule having a *functional equivalency* to the synthetic multivulval genes. It would be readily apparent to a skilled artisan in the field that since all of the possible functions of the synthetic multivulval gene products are not known, it would be impossible to know what molecules would be considered to be functional equivalents. Conversely, even if the exact function for the ortholog was defined, it would be impossible to know all of the molecules that might have that function.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claim(s) 1-4

is/are broad and generic, with respect to all possible compounds encompassed by the claims. The possible structural variations are limitless to any "ortholog". Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of the genes for *lin(n3628)*, *lin(n4256)*, *lin-65* and *mep-1* and compounds identified in the specification tables and/or examples, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for identifying a compound that may have potential as a compound that treats a neoplasia, comprising: contacting a *C. elegans* vulval precursor cell comprising a "loss of

function" mutation in a Class B synMuv gene and a second "loss of function" mutation in a "Class A synthetic multivulval gene" (or functional ortholog thereof), with a candidate compound,

does not reasonably provide enablement for a method for identifying a compound that treats a neoplasia. In addition, the specification does not reasonably provide enablement for any cell type (instant claim 1, step a) or for any cell in a nematode (instant claim 2) or for any isolated mammalian cell (instant claim 3). Furthermore, the specification does not reasonably provide enablement for *any type of gene mutation* in a Class B synMuv gene from the listed genes (instant claim 1, step a) or for *any type of second mutation* in a synthetic multivulval gene, or an ortholog thereof (instant claim 1, step a). In addition, the specification does not reasonably provide enablement for *any* type of phenotypic alteration (instant claim 1, step b). Furthermore, the specification does not reasonably provide enablement for the conclusion that any phenotypic alteration which is a decrease in cell proliferation (instant claim 4) is an indication that the candidate compound would be a compound that *treats* a neoplasia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 1 is directed to a method for identifying a compound that treats a neoplasia, said method comprising: (a) contacting a cell comprising a first mutation from the group consisting of: mep-1, lin(n3628), lin(n4256), and lin-65 and a second mutation in a synthetic multivulval gene, or (or an ortholog thereof), with a candidate compound; and (b) detecting a phenotypic alteration in said contacted cell relative to a control cell, wherein a candidate compound that alters the phenotype of said contacted cell relative to said control cell is a compound that treats a

neoplasia. Claims 2 and 3 are directed to claim 1 and further directed to wherein the cells are in a nematode (claim 2) or in isolated mammalian cells (claim 3). Claim 4 is directed to claim 1 and further to wherein the alteration in phenotype is a decrease in cell proliferation.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)). The following factors are relevant in the instant case:

Nature of the invention: The nature of Applicant's invention involves determination of potential anti-neoplastic activity by a process involving contacting a mutant cell with a candidate compound and detecting a phenotypic alteration in said contacted cell relative to a control cell. While the nature of this experiment is technologically feasible within a certain limited scope, the results of performing this assay would not necessarily identify a compound having anti-neoplastic activity and the scope of the claims extends well beyond the scope enabled by the application.

Breadth of the claims: The breadth of Claim 1 would allow a skilled artisan to perform the method as claimed in so many different ways as to achieve opposing experimental results

depending on the broad experimental conditions one might choose to use. Claim 1 recites "contacting a cell" which reads on all cell types. However, the model for the synMuv Class A and Class B mutants is performed using precursor vulval tissue in the nematode *C. elegans* (see especially specification). Even the breadth of the more limiting dependent claims 2 and 3, which read on *any* cell in a nematode or in an isolated mammalian cell, would still be too broad to ensure the same outcome which is obtained using synMuv mutants in the precursor vulval tissue of *C. elegans*. Claim 1 also reads on *any* first mutation and any second mutation but the use of a "loss of function" mutation, or a "gain of function", or "non-functional" mutation would all result in different outcomes of this method. Claim 1 also reads broadly on a second mutation in a synMuv gene but the specification clearly teaches that the synMuv Class B gene must accompany the synMuv Class A mutation because of the functional redundancy of the synMuv Class A genes. Claim 1, as stated, reads so broadly that a person of skill in the art might perform the instant method using a first and second mutation in the same gene in the same construct which would have the effect of only a single mutation. Claim 1 also reads broadly on *any* phenotypic alteration that could occur in said cells as a result of contact with said candidate compound. However, it is not indicated how *any* alteration in said cell's phenotype (claims 1-3), which occurs as a result of contacting said cells with *any* candidate compound, in comparison to a control cell could be interpreted to indicate that the said compound is therefore a compound that treats a neoplasia.

State of the Prior Art and Predictability: The state of the prior art teaches that the SynMuv phenotype is revealed when mutations are present in genes from both classes A and B. Several

class B genes have been identified as components of the Rb transcriptional regulatory-complex and "this finding raises the possibility of cross talk between cell-cycle/transcriptional controllers and known regulators of vulval development including members of the RTK/Ras/map kinase pathway. (Fay and Han), "The Synthetic Multivulval Genes of C. elegans: Functional Redundancy, Ras-Antagonism, and Cell Fate Determination", in Genesis: 26:279-284 (2000). Fay and Han further point out that "multiple mechanisms could be operating in the generation of the SynMuv phenotype. This possibility seems even more likely given that two distinct classes of mutants are required for the expression of the phenotype. the basic observation that class A and B genes are genetically redundant does not mean that both classes carry out identical biological functions. Malfunctions in two distinct pathways could converge to produce the observed defect. For example, the combination of cell-cycle and transcriptional defects could interfere with cell fusion, if both timing and gene expression are critical to this process. Clearly more work will be necessary to sort out these possibilities and provide a more precise picture of how these processes relate to one another." (p. 283, ¶ 4).

Furthermore, the state of the prior art teaches that the use of isolated mammalian cells are not predictable models of cancer. For example, Zips *et al.* ["In Vitro and In Vivo Evaluation of new Anticancer Agents" In Vivo. 2005 Jan-Feb;19(1):1-7] recites:

> "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Vascularisation, perfusion and, thereby drug acccess to the tumor cells are not evenly distributed and this fact 'consists' an important source of heterogeneity in tumor response to drugs that does not exist *in vitro*. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluation in animal tumor systems is essential." (p.3 col.2)

Because of the reasons stated above, the unpredictability of the outcome of the neoplasia assay would require undue experimentation with various cell types to determine whether the assay would be able to identify putative neoplastic agents. Therefore, the claims are properly rejected under 35 USC § 112, first paragraph, as lacking an enabling disclosure.

Direction provided by the inventor and Existence of working examples: For the instant invention, the applicant does not provide direction or evidence of working examples to establish whether the invention is enabled for all cell types, all mutation types, all orthologs and all types of phenotype alterations (claim 1). Therefore, the skilled artisan seeking to practice the invention according to its full scope would not be able to predict which embodiments within the broad scope of the claims could be used as claimed. Therefore, the skilled artisan must experimentally determine which cells, orthologs, and mutations to use in Applicant's method for claim 1. For these reasons, undue experimentation would be required to use the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a)/(e), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duyk *et al.* (US Patent No.6,531,644 B1, filed 20 January 2000) and further in light of Unhavaithaya *et al.* "Mep-1 and a Homolog of the NURD Complex Component Mi-2 Act Together to Maintain Germline-Soma Distinctions in C. elegans" Cell, Vol 111, Issue 7 27 December 2002, p. 991-1002).

Claim 1 is directed to a method for identifying a compound that treats a neoplasia, said method comprising: (a) contacting a cell comprising a first mutation in a Class B synMuv gene selected from the group consisting of: mep-1, lin(n3628), lin(n4256), and lin-65 and a second mutation in a synthetic multivulval gene, or (or an ortholog thereof), with a candidate compound;

and (b) detecting a phenotypic alteration in said contacted cell relative to a control cell, wherein a candidate compound that alters the phenotype of said contacted cell relative to said control cell is a compound that treats a neoplasia.

Duyk *et al.* teaches a method comprising: (a) contacting a cell comprising a first mutation in a Class B synMuv gene and a second mutation in a synthetic multivulval gene, or (or an ortholog thereof), with a candidate compound; and (b) detecting a phenotypic alteration in said contacted cell relative to a control cell, wherein a candidate compound that alters the phenotype of said contacted cell relative to said control cell is a compound that treats a neoplasia. For example, Duyk *et al.* teaches mutations in Rb or Rb-like genes, and in the lin-12 and lin-31 genes (specification col. 26, ¶ 1-4 and col. 4, ¶ 3, lines 1-12). "Alternatively, anti-tumor agents can be identified by administering various compounds directly to the transgenic animals, or their progeny and selecting as putative therapeutic agents, compounds that result in target-tissue specific antiproliferation." (see especially reference abstract lines 16-20). "Compounds that cause a reduction in size of the target tissue and have no adverse effects on non-target tissues are further evaluated as putative anti-tumor compounds" (see Duyk *et al.* specification, col. 5/6, ¶ 5/1).

Duyk *et al.* teaches using Class B synMuv mutants but fails to explicitly teach one of the Class B synMuv mutant genes: Mep-1 gene, lin(n3628), lin(n4256), or lin-65.

Unhavaithaya *et al.* (see abstract) teaches using a mutated MEP-1 gene for double-mutant Class B synMuv pathway experiments.

One would have been motivated at the time the invention was made and it would have been obvious to one of ordinary skill in the art at the time the invention was made to have

utilized an MEP-1 mutant gene for a representative Class B synMuv mutant gene, as taught by Unhavaithaya *et al.*, in the method taught in Duyk *et al.* because Unhavaithaya *et al.* teaches that "just as embryonic somatic cells require MEP-1 and Let-418 to stably inactivate germline potential, we propose that the activities of MEP-1 and LET-418 and, by extension, other synMuvB proteins including HAD-1 are required during larval development for VPCs to stably inactivate the potential to undergo vulval differentiation (p. 999, ¶ 1, lines 9-24)." Furthermore, A skilled artisan would have been motivated to use the MEP-1 mutants of Unhavaithaya *et al.* in the method of Duyk *et al.* because Unhavaithaya *et al.* teaches that the MEP-1 gene products are critical components of cell proliferation/differentiation pathways: "When the gonad signals the VPCs to initiate vulval differentiation, synMuvB components, including MEP-1, LET-418, and HAD-1, are either down-regulated in the three VPCs nearest the gonadal signal or are activated in more distal VPCs. SynMuvB activity in the three VPCs not selected to undergo vulval development inactivates the previously set chromatin-based potential to undergo vulval differentiation and ensures that these cells instead undergo the alternative pathway of fusion with the hypodermal syncytium. (p. 999, ¶ 1, lines 9-24).

Both Duyk *et al.* and Unhavaithaya *et al.* are in the field of developmental genetics and both are directed to methods which use synMuv Class B multivulval gene mutations to dissect pathways in cell proliferation.

Absent evidence to the contrary, one would have a reasonable expectation of success combining the teachings of the art because the use of MEP-1 mutant genes for representative Class B synMuv mutants for studying cell proliferation pathways was successfully practiced at the time the teachings of Duyk *et al.*, and Unhavaithaya *et al.* were published.

Claims 2 and 4 are directed to the method of claim 1 and further to wherein said cell is in a nematode (claim 2), or wherein said phenotypic alteration is a decrease in cell proliferation (claim 4).

Duyk *et al.* teaches wherein said cell is in a "C. elegans" nematode, "wherein C. elegans is used and the target tissue is selected from the group consisting of vulval, muscle, and nerve tissue" (see reference claims 1, 6 and 18).

Duyk *et al.* further teaches wherein said phenotypic alteration is a decrease in cell proliferation. "Alternatively, anti-tumor agents can be identified by administering various compounds directly to the transgenic animals, or their progeny and selecting as putative therapeutic agents, compounds that result in target-tissue specific antiproliferation." (see especially reference abstract lines 16-20).

In view of the foregoing, the method of claims 1, 2,and 4, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC *§103(a)/(e).*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine S. Hibbert whose telephone number is 571-270-3053. The examiner can normally be reached on Monday-Friday, 7:30 AM-5:00 PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mary Mosher can be reached on 571-272-0906. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner: Catherine S. Hibbert

DANIEL M. SULLIVAN, PH.D.
PRIMARY EXAMINER